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10/534,355	05/09/2005	Claude Dal Farra	0591-1008	4931

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EXAMINER	
MOHAMED, ABDEL A	
ART UNIT	PAPER NUMBER
1654	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/534,355	DAL FARRA ET AL.	
	Examiner	Art Unit	
	ABDEL A. MOHAMED	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-7,13,14 and 16-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-7,13,14 and 16-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

ACKNOWLEDGMENT TO AMENDMENT, REMARKS AND STATUS OF THE CLAIMS

1. The amendment and remarks filed 02/04/08 are acknowledged, entered and considered. In view of Applicant's request claims 1, 2, 4-7, 13, 14 and 16-20 have been amended and claims 3 and 15 have been canceled. Claims 1, 2, 4-7, 13, 14 and 16-20 are now pending in the application. The objection to the specification and the rejections under 35 U.S.C. 112, second paragraph, 35 U.S.C. 102(b) and 35 U.S.C. 103(a) over the prior art of record are withdrawn in view of Applicant's cancellation of claims, amendment and remarks filed 02/04/08. However, the objection to the claims and the rejection under 35 U.S.C. 112, first paragraph are maintained for the reasons of record. The rejections over the prior art of record has been considered but deemed to be moot in view of the new ground of rejections as set forth *infra*.

ARGUMENTS ARE NOT PERSUASIVE

OBJECTION OF THE CLAIMS

2. It is noted that Applicant has amended claims 4 and 16 to recite "a concentration ranging from approximately **0.05** and 500 ppm" by canceling "between" and adding "from". However, as suggested in the previous Office action amendment of the claims to recite "a concentration ranging from approximately **0.005** to 500 ppm" would obviate

this objection. The amendment does not remedy the deficiency, so the objection is maintained.

CLAIMS REJECTION-35 U.S.C. 112, 1st PARAGRAPH

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 7 remains under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant has argued that claim 7 has been amended to recite a method for increasing lipolysis into adipocytes and asserted that it is clearly supported in the present specification of page 8, lines 15-25 and Example 6. Contrary to Applicant's argument and assertion there is no showing for a method for increasing lipolysis in adipocytes, comprising administering to a subject in need of treatment thereof an effective amount of a composition according to claim 13 in the manner claimed in claim 7. Page 8, lines 15-25 of the specification defines the triglyceride-lipase activity as well as lipolysis and their relationships with respect to the degree of lipolytic activity of the

peptide. Example 6 measures the increase in the concentration of cAMP, in adipocytes, in order to determine the activation of the phenomenon of lipolysis.

Therefore, the specification fails to disclose a method for increasing lipolysis in adipocytes, comprising administering to a subject in need of treatment thereof an effective amount of a composition according to claim 13 because claim 7 is directed to *in vivo* treatment while the support Applicant cites and Example 6 are directed to *in vitro*. Thus, the Examiner reiterates the previous Office action.

There is no description in the instant specification for the claimed method for **increasing lipolysis in adipocytes**, comprising administering to a subject in need of treatment thereof an effective amount of a composition according to claim 13 as claimed in claim 7. The specification demonstrates synthesis of the claimed peptide and various *in vitro* assays in various cells. Examples 1-4 demonstrate the effect of the peptide on various cells *in vitro* assays. Example 5 shows the activity of the peptide on adipocytes *in vitro*, and Example 6 shows the activity of the peptide on the amount of intracellular cAMP *in vitro* while Example 7 disclose the method of the preparation of the claimed compositions. However, there is no pharmaceutical formulation administered to a subject in need of treatment thereof an effective amount of a composition according to claim 13 containing an acceptable medium as an active ingredient, at least a peptide of formula (I): (AA)n-Arg-Gly-Ser-(AA)n (I) wherein (AA) is unspecified amino acid or one of its derivatives, and n is an integer ranging between 0 and 3 as claimed in claim 7. There is no *in vivo* showing for the effectiveness of the method for **increasing lipolysis in adipocytes**, comprising administering to a subject in need of treatment thereof an

effective amount of a composition according to claim 13 in the manner claimed in claim 7. Thus, the specification does not satisfy the written description requirement of 35 U.S.C. 112, first paragraph with respect to the full scope of claim 7.

NEW GROUNDS OF OBJECTION AND REJECTIONS

OBJECTION OF CLAIMS

4. Independent claims 1 and 13 and claims dependent thereof are objected in the recitation "and N is an integer". It is believed to be typographical error. Amendment of the claims to recite "and n is an integer" as disclosed in formula I is suggested.

Also, claim 6 is objected in the recitation "is" twice in lines 2 and 4, respectively. Deletion of one "is" would obviate this objection.

CLAIMS REJECTION-35 U.S.C. 103(a)

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4-6, 13, 14 and 16-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al (Biochemistry, Vol. 35, No. 1, pp. 197-201, 1996) taken with either Hortin et al (Biochemistry International, Vol. 26, No. 4, pp. 731-738, 1992) or WO 2000-77042, published December 21, 2000 (referenced as Usdin et al US-PGPUB 2003/0032096). Liu et al and '096 patent were cited in the previous Office action.

The primary reference of Liu et al discloses the isolation of a tripeptide such as Arg-Gly-Ser (RGS) peptide, which inhibits binding of mAb TL4 to its membrane receptor. The reference clearly teaches that RGS peptide is contemplated in a pharmaceutical composition that inhibits binding of mAb TL4 to its membrane receptor by using various concentrations of RGS peptide, which overlaps with the claimed ranges of concentrations ranging from 0.005 to 500 ppm. The reference states that the peptides were purified by affinity purification (See e.g., abstract), and which necessarily requires that the peptide be "solubilized", and thus meeting the limitations of claims 5 and 18.

The primary reference of Liu et al differs from claims 1, 2, 4-6, 13, 14 and 16-20 in not **explicitly** teaching the use of protective groupings in the form of an amidation of the carboxy-terminal end, use of solvents and formulations thereof. However, the secondary reference of Hortin et al describes a simple combinatorial approach to prepare much larger members of peptides by synthesizing them as complex mixtures, wherein using 65 couplings of single amino acids, five mixtures were prepared with the sequences Try-Gly-Arg-Gly-Yyy-Xxx-Xxx, where Yyy is Ser, Asp, Arg, Asn, or Glu, and Xxx is any amino acids. The reference also, shows the use of protective group such as t-butyloxycarbonyl (Boc). See e.g., pages 731 and 732, Summary, Introduction, Materials and Methods, Table 2 and Discussions. Thus, the secondary reference of Hortin et al clearly discloses the preparation of a composition comprising an active ingredient of at least reference of formula I: (AA)n-Arg-Gly-Ser-(AA)n, wherein (AA) is unspecified amino acid, n is an integer ranging between 0 and 3, and wherein said peptide has a protective in the form of amidation of carboxy-terminal end.

Further, the secondary reference of Usdin et al (PGPUB '096) teaches that the N-terminus may be any of the groups: amino, hydrophobic, acetyl, 9-fluorenylmethoxy-carbonyl (FMOC), or macromolecular group (See e.g., paragraph 0052). The C-terminus may be a carboxyl group, an amide group, a T-butyloxycarbonyl group or a macromolecular carrier group (See e.g., paragraph 0053).

Furthermore, the secondary reference of '096 patent teaches that pharmaceutical compositions where the peptide fragments, and analogs of the invention can be employed in admixture with conventional excipients, i.e., pharmaceutically acceptable

organic or inorganic carrier substances suitable for parenteral, enteral or topical applications that do not deleteriously react with the active peptides, fragments, and analogs of the invention. Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions, alcohols, gum Arabic, vegetable oils, benzyl alcohols, polyethylene glycols, gelatin, carbohydrates such as lactose, amylase or starch, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, etc. Further, the '096 reference states that the pharmaceutical preparations can be sterilized and if desired mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, flavoring and/or aromatic substances and the like which do not deleteriously react with the above compounds. They can also be combined where desired with other active agents, e.g., vitamins (See e.g., paragraph 0100).

Moreover, the secondary reference of '096 patent teaches that sustained or directed release compositions can be formulated, e.g., liposomes or those wherein the active compound is protected with differentially degradable coatings, e.g., by microencapsulation, multiple coating, etc. (See e.g., paragraph 0103), and, for topical application, there are employed as non-sprayable forms, viscous to semi-solid or solid forms comprising a carrier compatible with topical application and having a dynamic viscosity preferably greater than water. Suitable formulations include but are not limited to solutions, suspensions, emulsions, creams, ointments, powders, liniments, salves, aerosols, etc., which are, if desired, sterilized or mixed with auxiliary agents, e.g., preservatives, stabilizers, wetting agents, buffers or salts for influencing osmotic

pressure, etc. For topical application, also suitable are sprayable aerosol preparations wherein the active ingredient, preferably in combination with a solid or liquid inert carrier material, is packed in a squeeze bottle or in admixture with a pressurized volatile, normally gaseous propellant, e.g., a Freon (See e.g., paragraph 0104). Thus, the teachings of '096 patent fully meets the limitations of claims 5, 6, and 18-20.

Therefore, both secondary references of Hortin et al and '096 patent teach modifications are suitable for the N and C termini of the compounds resulting in a peptide having a protective group in a form of amidation of the carboxy-terminal end. Thus, one of ordinary skill in the art to which this invention pertains would have been motivated to select an N- or C-terminally modified compound, with a reasonable expectation of success, because the compounds are disclosed as capable of being modified.

Further, the secondary reference of '096 patent discloses the peptides may be formulated for pharmaceutical applications, one formulation being dermatological. Also, in regard to pharmaceutical composition, to the extent that RGS is in a physiological buffer it is considered to be a pharmaceutical composition (See e.g., page 199, right column of the primary reference of Liu et al and under Materials and Methods of the secondary reference of Hortin et al). Therefore, it would have been obvious to one of ordinary skill in the art to select suitable delivery agent for administration of the peptide of interest, and one would have been motivated to combine the peptides in a pharmaceutically acceptable composition, with a reasonable expectation of success, as

the compounds disclosed as being capable of prepared for administration in pharmaceutically acceptable solvents.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the peptides of the primary reference in the methods of secondary references of Hortin et al or '096 patent because as discussed above the methods of Hortin et al and '096 patent clearly disclose the preparation of pharmaceutical formulation of any peptide of interest, including RGS (See Hortin et al), the use of protective groupings in a form of an amidation of the carboxy-terminal end, the use of solvents, and wherein the pharmaceutical formulation is capable of being administered topically. Thus, from the combined teachings of the prior art, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the combined teachings of the references, which fall with the scope of the prior art method and composition would have been obvious because as held in host of cases including *Ex parte Harris*, 748 O.G. 586; *In re Rosselete*, 146 USPQ 183; *In re Burgess*, 149 USPQ 355 and as exemplified by *In re Betz*, "the test of obviousness is not express suggestion of the claimed invention in any and all the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them".

ACTION IS FINAL, NECESSITATED BY AMENDMENT

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

CONCLUSION AND FUTURE CORRESPONDANCE

7. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ABDEL A. MOHAMED whose telephone number is (571)272-0955. The examiner can normally be reached on First Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mohamed/A. A. M./
Examiner, Art Unit 1654

/Jon P Weber/

Supervisory Patent Examiner, Art Unit 1657